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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/539,821	12/14/2005	Vittorio Dal Piaz	09605.0011	5918

22852 7590 09/19/2007

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
09/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/539,821	DAL PIAZ ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21,23 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *19-21* is/are allowed.

6)☒ Claim(s) *1-15,23, 26, 27 abd 29* is/are rejected.

7)☒ Claim(s) *16-18 and 28* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-01-06, 08-07-06 & 07-23-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Rejections Under 35 US 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling treatment of asthma and atopic dermatitis with Formula (I) compounds, does not reasonably enable treatment of all pathological conditions/diseases susceptible to amelioration by PDE-4 inhibition with Formula (I) compounds (claim 26) or treatment of asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis and irritable bowel disease. The present specification offers no evidence that the claimed compounds control such specific diseases/conditions, although these claims encompass such diseases/conditions. The specification otherwise does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the

inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for hepatitis B surface antigen detection did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. The claims cover potentially billions of compounds of Formula (I).

(b) Scope of the diseases covered. Claim 26 is directed to a method for treating a condition or disease susceptible to amelioration by inhibition of PDE-4, including respiratory disease (broadly), inflammatory bowl disease (IBD), skin disease (broadly), MS and osteoporosis, mentioned by Spina, Drugs, 2003, 63, 23, pp. 2575-2594, and other undiscovered disorders/conditions that may be associated with PDE-4 now or in the future, for which the disclosure is non-enabling. The claimed scope includes the recited disorders as well as undiscovered disorders/conditions associated with PDE-4 for which there is no enabling disclosure. The full scope of claim 26 is unknown.

Claim 27 is directed to methods for treating asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, atopic dermatitis, psoriasis and irritable bowel disease. The claimed scope includes treating various disorders/diseases,

which are inadequately enabled, based on inhibition of PDE-4. The compounds of Formula (I) are disclosed to inhibit PDE-4 and the specification recites that these compounds are therefore useful to treat all diseases susceptible to amelioration by PDE-4 inhibition, such as diseases mentioned by Spina, for which Applicants provide no competent evidence.

Chronic Obstructive Pulmonary Disease (COPD) (claim 27) is a collection of progressive airway diseases, characterized by gradual lung function loss. COPD includes chronic obstructive bronchitis (inflammation and eventual scarring of the bronchi) and emphysema (enlargement and destruction of the alveoli). Emphysema comes in several forms, including congenital lobar emphysema, bullous emphysema, centrilobular emphysema (proximal acinar emphysema), panacinar (panlobular), distal acinar (paraseptal) as well as Alpha-1 antitrypsin (AAT) deficiency, a genetic form of emphysema. COPD patients often have both bronchitis and emphysema. Ordinary chronic bronchitis is sometimes included with COPD even if there is no actual obstruction, and asthmatic bronchitis is generally included in COPD as well. Persons with COPD typically develop smaller air passageways, which can become clogged with mucus and have partially destroyed alveoli.

IBD (claim 27) is generic to a family of disorders, of which ulcerative colitis and Crohn's disease are most important. Less common forms are colitis (including lymphocytic, collagenous, diversion, ischemic and infective colitis), radiation enterocolitis, solitary rectal ulcer syndrome (SRUS), antibiotic associated IBD and Behçet's Syndrome. IBD has a range of known and unknown causes. Ulcerative

colitis, Behçet's Syndrome and Crohn's disease, e.g., are idiopathic. Partial tissue death (infarct) due to blood supply blockage, e.g. after major abdominal surgery or poor cardiac output in heart disease, can cause ischemic colitis. Cancer therapy can cause radiation enterocolitis. Infective colitis can arise from bacteria (e.g. shigella, salmonella, campylobacter, E. coli) or viruses (e.g. Norwalk-like virus rotavirus, CMV, HSV). Fecal stream diversion after ileostomy or colostomy can cause diversion colitis. Treatment depends on form, and some, e.g., radiation enterocolitis and SRUS, have no current effective pharmaceutical treatment.

The claims also cover asthma, rheumatoid arthritis, atopic dermatitis and psoriasis.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

The claims are directed to therapeutic use of the claimed compounds in ameliorating diseases/conditions related to PDE-4 activity. The various types of PDE-4 generally arise from the presence or absence of two unique N-terminal domains called upstream conserved regions 1 and 2 (UCR1 and 2) and other pieces that may be present. UCR1 and UCR2 have been shown to form a module necessary for activation of PDE-4 upon phosphorylation by cAMP-dependent kinase (PKA). For example, there are at least five different forms of PDE-4B: PDE-4B1,

PDE-4B2 (the short form), PDE-4B3, PDE-4B4 and very recently discovered, PDE-4B5. Distinct PDE-4A isoforms include PDE-4A1, PDE-4A5, PDE-4A4B, PDE-4A7, PDE-4A8, PDE-4A10 and PDE-4A11. PDE-4D has nine forms, 1-9. These various forms are not necessarily interchangeable and there is substantial variation in distribution even within the sub-families. Thus, PDE-4A1 is abundant in the brain, PDE-4A4B and PDE-4A10 in inflammatory cells, PDE-4A7 in the brain and spleen, and PDE-4A11 is widely distributed. The PDE-4D family is generally not seen in inflammatory cells at all. PDE-4D1 is seen in the spleen and heart, PDE-4D2 in the spleen, PDE-4D3 in brains, lung and kidney, PDE-4D4 and PDE-4D6 in the brain, PDE-4D5 in the lung and kidney, PDE-4D7 in the brain and testes, PDE-4D8 in the lung, heart and liver, and PDE-4D9 in the spleen, heart and lung. Different types are regulated differently as well. ERK MAP kinases phosphorylate and regulate the activity of PDE-4B, PDE-4C and PDE-4D but not PDE-4A isoforms. Reduced PDE-4D activity apparently causes defective RyR2-channel function associated with heart failure and arrhythmias. In dendritic cells (the cells responsible for the priming of naive T_h cells), PDE-4A is predominantly active, whereas monocytes mainly express PDE-4B. PDE-4D5 isoform preferentially interacts with the signaling scaffold proteins, β-arrestin and RACK1. PDE-4D3 likewise forms a signaling complex with AKAPs such as AKAP450. See the discussion of phosphodiesterase in Wikipedia.

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (Fed.Cir. 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for conditions other than asthma and atopic dermatitis
4. **State of the prior art:** These compounds are amino pyridazin-3(2H)-ones with a particular substitution pattern.
5. **Working Examples:** No examples show treatment of any disorder. The sole biological data demonstrates only PDE4 inhibition, and which PDE4 subtype tested is not indicated. Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claimed compounds.

The compounds are disclosed to inhibit PDE-4 activity and the specification recites that these compounds are therefore useful to treat all diseases susceptible to amelioration by inhibition of PDE-4, such as asthma, COPD, rheumatoid arthritis, atopic dermatitis, psoriasis or IBD, for which Applicants provide no competent evidence. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for the intended host.

6. Skill of those in the art: The specification indicates that these compounds are potent and selective inhibitors of phosphodiesterase 4 (PDE4) and are thus useful in the treatment, prevention or suppression of pathological conditions, diseases and disorders known to be susceptible of being improved by inhibition of PDE4. The concept that PDE-4 inhibitors could treat such pathological conditions/diseases generally is contrary to what is known about PDE-4 inhibitors. Some PDE4 inhibitors cause vasculitis (blood vessel inflammation), which has hindered PDE-4 inhibitor clinical investigation. Development of SCH-351591 halted because of acute and chronic vasculitis in small to medium sized arteries, and vasculitis was a significant problem with CI-1018 and Ariflo® (cilomilast). The PDE-4 inhibitor IC542 triggered a generalized inflammatory response with extensive neutrophil infiltration in the gastrointestinal tract, nearby mesentery and thymus.

The state of the art (e.g., MacKenzie, Alergology International (2004) 53: 101-110, and the discussions of Dyke, Exp. Opin. Invest. Drugs, 8(9):1301-1325, 1999, Stawiski, J. Invest. Derm., 73(4), 261-263, 1979, Hanifin, J. Invest. Derm., 107(1), 51-56, 1996, Griffiths, Brit. J. Derm., 2002, 147, 299-307, Spina, Drugs, 2003, 63, 23, pp. 2575-2594, and other references discussed in detail below) supports that successful amelioration of conditions caused or exacerbated by PDE-4 is a subject for further investigation. See the discussion of PDE-4 above.

Regarding IBD, treatment depends on form, and some forms, e.g., radiation enterocolitis and SRUS, have no current effective pharmaceutical treatment. Many if not most diseases said to be ameliorated by inhibition of PDE-4, e.g., allergic rhinitis,

osteoarthritis, osteoporosis, bone-formation disorders, glomerulonephritis, multiple sclerosis, ankylosing spondylitis, Graves ophtalmopathy, myasthenia gravis, diabetes insipidus, graft rejection, gastrointestinal disorders, ulcerative colitis, Crohn's disease, septic shock, adult distress respiratory syndrome, atopic dermatitis, contact dermatitis, acute dermatomyositis, dementia, Alzheimer's disease, depression, etc., are known as difficult to treat. At present no known drug can successfully prevent or reverse the course of many of these diseases, despite the fact that many drugs are said to inhibit PDE-4.

Baumer, et al., Inflammation & Allergy – Drug Targets, Vol. 6, No. 1, Mar. 2007, pp. 17-26 (10), report testing with PDE4 inhibitors in treatment of psoriasis, and conclude, "Results concerning clinical efficacy of this potent and selective PDE4 inhibitor [AWD 12-281 (GW 842470)] are anxiously awaited." Implications for Rheumatoid Arthritis http://www.medscape.com/viewarticle/464104_4, downloaded July 8, 2007, reports, for potential treatment of rheumatoid arthritis, "...the possibility of a combined approach using VIP together with a PDE inhibitor merits further investigation." These articles both demonstrate that enablement for such utilities was not established as of the date of filing.

COPD has no pharmaceutical treatment *per se*. Instead, treatment is supportive and designed to relieve symptoms and improve quality of life. Thus, oxygen is often given to partially compensate for lung function loss. Bronchodilators can expand lung passageways, corticosteroids can reduce inflammation and antibiotics can ward off bacterial infections, but none of these treat COPD itself.

The art indicates the level of unpredictability. MacKenzie indicates that, although the newer PDE-4 inhibitors "display greatly reduced side-effects, ... further study of the potential ancillary involvement of adrenaline and/or glucocorticoids in the enhancement of PDE-4, shown in blood mononuclear white cells of [atopic dermatitis] patients is warranted." Thus, the ability of an agent that inhibits PDE-4 to ameliorate all of the diseases/conditions recited by the present claims remains open to further study and proof.

The history of the actual effectiveness of PDE-4 inhibitors is very short. PDE-4 inhibitors have been investigated for disorders ranging from AD to COPD to depression to schizophrenia to chronic lymphocytic leukemia (CLL). Except in the area of asthma, such efforts have met with very little success. As of the time of filing, and indeed up to now, the FDA has not approved any PDE-4 inhibitor for treatment of any disorder. Extensive effort to get cilomilast and Daxas® (roflumilast) to be effective against COPD has been without success, evidence of the skill level in this art. Whether these claimed compounds affect the same isoenzymes as cilomilast and roflumilast is not described.

7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to make and use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art indicates the requirement for undue experimentation. MacKenzie indicates that, although the new generation of PDE-4

inhibitors "display[s] greatly reduced side-effects, ... further study of the potential ancillary involvement of adrenaline and/or glucocorticoids in the enhancement of PDE-4, shown in blood mononuclear white cells of [atopic dermatitis] patients is warranted." The ability of an agent that inhibits PDE-4 to ameliorate all diseases or conditions recited by the present claims remains open to further study and proof.

Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses. Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* The disclosure in this application is not sufficient to enable the instantly claimed methods based solely on disclosure of inhibition of PDE-4 by compounds of Formula (I).

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (Fed.Cir. 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention. The consideration of the above factors demonstrates that the present application does not sufficiently enable the present claims. In view of the breath of the claims, the pharmaceutical

nature of the invention, the unpredictability of relationship between PDE-4 and specific diseases/conditions, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Rejections Under 35 USC 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-15, 23 and 29 are rejected under 35 USC 102(b) over Dal Piaz, et al., J. Pharm. Sci. Vol. 80, No.4, April 1991, 341-348 (hereafter Dal Piaz, cited by Applicants). See Table III, page 344, Compound 4g. The compound is active in carrageenin-induced rat paw edema.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-15, 23 and 29 are rejected under 35 USC 102(e) as obvious over WO 03/097613 to Dal Piaz, et al., entitled to the International Filing Date of May 14, 2003 (hereafter Dal Piaz II, cited by Applicants). See Compounds 1 – 274 in Table 2, pages 44-78. Dal Piaz II describes the compounds as inhibitors of phosphodiesterase 4.

Allowable Subject Matter

Claims 16-18 and 28 are objected to as dependent on a rejected claim but would be deemed allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. Claims 19-21 are allowed.

The two Dal Piaz references applied above do not show the particular substitution patterns of the compounds of these claims, their method of preparation or their specific compositions.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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